REMARKS AND ARGUMENTS

Amendments to the Claims

Claims 31 to 53 and 55 to 67 are currently pending in the application. Claims 31-45, 53, and 55-62 are withdrawn in response to the restriction requirement or election of species requirement. Claim 54 has been canceled without prejudice to future filing. Claims 46 to 52 and 63 to 67 are currently undergoing prosecution. Claim 46 is amended to more clearly recite the subject matter considered to be the invention. Claim 67 is also amended to recite specific SEQ ID NO: 18. Basis for the amendment to claim 67 is found in the specification, for example, on page 17, line 20 to page 18, line 4. Therefore, no new matter is presented by the amendments to the claims, and entry of the amendments to the claims is respectfully requested.

Rejections on the Basis of 35 U.S.C. § 112

Claim 67 stands rejected on the basis of 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to recite a specific SEQ ID NO:. This rejection is respectfully traversed. Claim 67 is amended as shown above to recite SEQ ID NO: 18. Therefore, Applicants respectfully request that the rejection of claim 67 on this basis be reconsidered and withdrawn.

Claims 46-49, and 63-67 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter that was not described or enabled in the application for reciting *preventing* or reducing chronic cardiotoxicity in independent claim 46. This rejection is respectfully traversed. Applicants point to the specification as filed, for example, page 2, lines 34 to 37, page 5, lines 17 to 24, and Example 7, pages 80 to 82, where it is demonstrated that blocking 4-1BB-L/4-1BB signaling *prevented* Adriamycin®-induced cardiomyopathy. As noted on page 81, lines 33-35, "...no mortality was observed in the 4-1BB-L KO mice and none of the 4-1BB-L KO mice showed signs of the most severe cardiotoxicity following Adriamycin® challenge compared to 50 to 71% of the wild type mice." On page 82, lines 7-8, the specification states: "These data [presented in Example 7] establish a sound basis for *preventing*, treating, or alleviating the symptoms of cardiovascular disease...". Therefore, it is clear from the application that antagonists capable of completely

blocking 4-1BB and 4-1BB-L signaling would prevent Adriamycin®-induced cardiomyopathy. Therefore, Applicants submit that the application describes and enables *preventing* as well as reducing chronic cardiotoxicity.

Claims 46-49 and 52 remain rejected on the basis of 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the application in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the claimed invention. This rejection is respectfully traversed. The Examiner has appeared to take the position that the application must contain a written description of every possible antagonistic of 4-1BB/4-1BB-L, its "complete or partial structure, physical and/or chemical properties, functional characteristics, methods of making" etc. (page 4, Office Action of 11/15/2007) in order to fulfill the written description requirement under 35 U.S.C.§ 112 with respect to claim 46. Applicants do not agree. It is not required that every possible embodiment of antagonist needs to be described to fulfill the requirements of 35 U.S.C.§112, first paragraph. Applicants point out that claim 46 recites a *method* of preventing or reducing chronic cardiotoxicity comprising administering a 4-1BB antagonist. The basis for this method is clearly found in the specification, for example, page 5, lines 17 to 24, wherein "antagonist" is defined functionally as a genus, and in Examples 7 and 8. In Example 7, data from experiments with knockout mice shown in Table 3 clearly "demonstrated that antagonizing 4-1BB-L:4-1BB interactions reduces Adriamycin®-induced cardiotoxicity". Clearly, the inventors had possession of the claimed method by identifying and demonstrating the connection between antagonizing 4-1BB-L:4-1BB signaling and preventing or reducing Adriamycin™-induced cardiotoxicity, as shown in the data of Example 7. This is the basis for the claimed method of claim 46, not a recitation of every possible antagonist of 4-1BB. Therefore, Applicants request that the Examiner reconsider and withdraw the rejection of claims 46-49 and 52 on the basis of 35 U.S.C. §112, first paragraph, written description.

Rejections under 35 U.S.C. § 103(a)

Claims 46-52 remain rejected under 35 U.S.C. §103(a) as allegedly unpatentable over the publication of Yndestad et al., and U.S. Patent 5,674,704 to Goodwin et al., in view of the Waelti U.S. published application 2004/0028687. This rejection is respectfully traversed.

The Examiner has alleged that one of ordinary skill in the art would have found the claimed methods obvious over the combination of the three cited references. Again Applicants do not agree for the following reasons. First, the Yndestad et al. and Goodwin et al. references in combination with Waelti do not teach or suggest the claimed methods. As stated in the Response submitted 5/14/2008, Yndestad et al. discloses that from 375 genes, 34 including 4-1BB were upregulated in the peripheral blood mononuclear cells from patients with *chronic heart failure* (CHR). The Examiner then states that Waelti mentions that doxorubicin causes dose dependent cardiotoxicity resulting in irreversible cardiomyopathy with serious congestive heart failure (page 3, paragraph 1). However, none of the patients screened in Yndestad et al. was suffering from chronic cardiotoxicity caused by a chemotherapeutic agent, specifically, an anthracycline drug, such as doxorubicin. Applicants do not agree that it would be obvious to one of ordinary skill to assume that the cardiotoxicity caused by doxorubicin would yield identical results to those found in Yndestad et al. for a different patient population which were noted to be "twenty patients with stable CHF" (page 176, third paragraph). Applicants further remind the Examiner, that in the restriction requirement of 4/10/2007, claims drawn to a method for reducing chronic cardiotoxicity (group II claims) were restricted from a method of treating cardiovascular disease, including chronic heart failure (group I claims), as distinct "because they are methods of treating different medical conditions, which are caused by different pathogens, and therefore involve distinct patient populations, have distinct clinical manifestations, distinct features in progress and prognosis, and require different therapies" (Office Action, page 2, mailed 4/10/2007). The instant claimed method is drawn to a method of preventing or reducing chronic cardiotoxicity caused by a chemotherapeutic agent, and yet the Examiner has cited as the primary reference a study of CHF patients. The Examiner has not provided any reference which provides evidence that one of ordinary skill in the art could assume or find it obvious that the increased gene expression found with CHF patients described in Ynedstad et al. would be the same for patients suffering from the chronic cardiotoxicity caused by doxorubicin. Indeed, the Examiner herself has characterized these two conditions as different, distinct medical conditions.

Second, Applicants submit the Examiner is relying on hindsight based on the disclosure in the instant application for the basis of her 35 U.S.C. § 103 (a) rejection, which is

not permissible in making a 103 rejection. Applicants point out that it was only the data contained in the instant application, such as the results from the studies of 4-1BB-L knockout mice injected with Adriamycin® in Example 7, and further studies described in Example 8, that demonstrated that antagonizing 4-1BB would prevent or reduce chronic cardiotoxicity caused by a chemotherapeutic agent. There is no reference provided by the Examiner that showed upregulation of 4-1BB for such a patient population. For these reasons, as well as the reasons previously set forth in the Response of 5/14/2008, Applicants request reconsideration and withdrawal of the rejection of claims 46-52 on the basis of 35 U.S.C. §103(a) as allegedly unpatentable over the publication of Yndestad et al., and U.S. Patent 5,674,704 to Goodwin et al., in view of the Waelti U.S. application 2004/0028687. Applicants' attorney invites the Examiner to call her at the number given below if it would be helpful in advancing the prosecution of this application.

Respectfully submitted,

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